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EVIDENCE-BASED REVIEW

Long-acting β_2 -agonists in asthma: an overview of Cochrane systematic reviews[☆]

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Summary According to major asthma management guidelines, long-acting β_2 -agonists (LABAs) should be used only when asthma remains symptomatic in patients already receiving regular inhaled corticosteroids (ICSs). A large Cochrane systematic review provides evidence that LABAs are safe and beneficial in control of asthma; sub-group analyses indicating that this is true when ICSs are used and in their absence. Two other Cochrane systematic reviews have found that LABAs are more effective than regular short-acting β_2 -agonists, and are as effective as theophylline with fewer side-effects. These reviews support guidelines in the use of LABA as additional therapy when asthma is inadequately controlled by ICS at moderate dose. However, guidelines may be too conservative, and more studies in stable mild asthma comparing their use and safety with placebo and ICS are required.

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Introduction

In this paper, we examine the evidence presented in Cochrane systematic reviews for the effectiveness and safety of long-acting β_2 -agonists (LABAs),

and assess the findings in the context of current national and international therapeutic management guidelines. In particular, we will review the evidence to support the use of LABA in their current role in conjunction with inhaled corticosteroid (ICS).

[☆] The following Cochrane reviews are cited in this evidence-based review: Walters EH, et al. Inhaled long-acting beta agonists for stable chronic asthma. The Cochrane Library, Issue 4, 2003; Walters EH, et al. Regular treatment with long-acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma. The Cochrane Library, Issue 3, 2003; Shah L, et al. Long-acting beta-agonists versus theophylline for maintenance treatment of asthma. The Cochrane Library, Issue 3, 2003.

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Inhaled β -agonist use

Inhaled β -agonists have been an integral part of asthma management for the past 50 years. Their main airway action is through engagement of G-protein-coupled β -receptors at the surface of smooth-muscle cells to induce muscle relaxation and, through that, bronchodilatation. Short-acting

β_2 -specific agonists (SABAs) have been available since the 1970s, and have a rapid onset and short duration of up to 4 h. They are used mainly for reactive "relief" of symptoms due to bronchoconstriction, and are effective and safe when used in this manner. LABAs, available for the past decade, were designed specifically for regular use, as their duration of action is at least 12 h. Their intended use is prospective, to prevent symptoms, whether spontaneous or due to some environmental or activity-related airway challenge. They have been termed "symptom controllers".

Inhaled corticosteroid use

The third class of widely used inhaled asthma medications is corticosteroids, which have disease-modifying actions through their anti-inflammatory effects. ICSs have been available since the 1960s, and have transformed the management of asthma. The currently accepted clinical wisdom is that, if a patient needs relatively frequent "relief" medication, then ICS should be introduced to gain "control" of the disease. The definition of "frequent" varies between management guidelines.¹⁻⁴ In reality, community-based audits have found that most asthmatics do not use ICS, even when quite symptomatic.⁵

Long-acting β_2 -agonists

Currently, two LABA agents are widely available, salmeterol and formoterol. They vary slightly in mode and length of action, but have clinically similar effects when used regularly.^{6,7} Salmeterol is a partial agonist,⁸ with slower onset of action, less total bronchodilator capacity at high dose, and also less likelihood to develop tachyphylaxis to bronchodilatation. Formoterol is a full agonist,⁹ with faster onset of action, greater bronchodilator efficacy in high dose, but with increased tachyphylaxis to smooth muscle relaxation.¹⁰ Both LABAs have been shown to develop tachyphylaxis to their bronchoprotective actions in inhibiting induced bronchoconstriction when used regularly at conventional doses, although some degree of protection remains.^{11,12}

In addition to their bronchodilator action, there is also evidence that LABAs have an anti-inflammatory and anti-remodelling effect on the airway in individuals already taking ICS.^{13,14} One mechanism may be through enhancing movement of the corticosteroid-corticosteroid receptor complex

from the cytoplasm to the nuclear compartment where it modulates cytokine and other gene transcription.^{15,16} The anti-inflammatory action seems especially evident in decreasing eosinophil infiltration of the airway wall,^{13,14} possibly by stimulating epithelial chemokine release into the airway lumen, so as to increase luminal cellular clearance.¹⁷

Concerns over β_2 -agonist use

Just at the time LABAs were being introduced, concerns about regular use of SABAs, the so-called " β -agonist debate", were at its height. A number of studies had implicated regular and perhaps excessive use of SABA in (1) asthma deaths and near-death emergencies;^{18,19} (2) worse clinical outcomes,^{20,21} and (3) induction of increased degrees of airway reactivity.^{22,23}

These concerns about adverse outcomes with frequent and regular SABA use are likely to have mainly been related to sub-optimal use of ICS in individuals whose asthma was inadequately controlled and treated.²⁴ However, the legacy of this debate led to an adverse sentiment against β -agonists in general, just at the time that clinicians needed to come to terms with the availability of LABAs, specifically designed and marketed to be used regularly in a 12-hourly regimen. This may have affected their subsequent clinical research development and placement in asthma management guidelines (Table 1).

Asthma management guidelines

In the Global Initiative for Asthma (GINA) guidelines,¹ which classify asthma by severity, recommendations for medication use are based upon different levels of disease severity. Their recommendation is to introduce LABA for moderate persistent asthma, together with regular ICS at "low to medium" dose. The Australian National Asthma Council guidelines² also suggest the use of LABA together with regular ICS in both adults and children based on disease severity. They recommend considering the addition of LABA to moderate doses of ICS for moderate disease and their use with high-dose ICS in severe disease. The BTS/SIGN³ guidelines use a different approach, based on disease activity. They recommend the addition of LABA where there is inadequate disease control on low-dose ICS. The full implementation of current guidelines remains the challenge for clinicians, yet

Table 1 International guidelines for long-acting β -agonist treatment in asthma.

GINA ¹	NAC ²	BTS/SIGN ^{3,4}
Moderate persistent	Moderate: with ICS up to 800 μ g/day	Inadequate control on low-dose inhaled steroids
Symptoms daily	Symptoms most days	The first choice as add-on therapy to inhaled steroids in adults and children (5–12 years) is an inhaled LABA
Nocturnal symptoms more than once a week	Exacerbations <6–8 weeks apart, which affect day-time activity and sleep	Inhaled LABA should not be used without ICS
Daily use of inhaled SABA FEV ₁ or PEF 60–80% predicted	Exacerbations last several days Occasional emergency department visit	
FEV or PEF variability over 30% Using low–medium dose ICS		
Severe persistent	Severe: with ICS up to 2000 μ g/day	
Symptoms daily	Persistent	
Frequent nocturnal symptoms	Limited activity level	
Limitation of physical activities	Nocturnal symptoms more than once a week	
FEV ₁ or PEF 60% \leq predicted	Frequent emergency	
Frequent exacerbations	Department visits and hospital admission in past year	
Using high-dose ICS	FEV ₁ may be significantly reduced between exacerbations	

BTS, British Thoracic Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; NAC, National Asthma Campaign; SIGN, Scottish Intercollegiate Guidelines Network; PEF, peak expiratory flow.

more research on the safety and effectiveness of LABAs at different levels of disease severity and activity is required. Indeed, in Australia, the NAC Management Handbook (2002)² states that “debate continues as to whether the regular long-term use of high-dose, SABA causes deterioration in asthma”, but concedes, “concerns about LABAs have not been clearly demonstrated in studies to date”. Nevertheless, the FDAs have sufficient anxieties about the use of salmeterol to have issued a “black box” warning on the medicine’s label.

Cochrane systematic reviews of interest

Three Cochrane systematic reviews directly relevant to the use of LABA in asthma have been published: (1) inhaled LABA for stable chronic asthma, first published in March 2003;²⁵ (2) regular treatment with LABA versus daily regular treatment with SABA in adults and children with stable

asthma, first published in January 2003;²⁶ (3) LABA versus theophylline for maintenance treatment of asthma, first published in August 1999.²⁷

Three relevant protocols^{28–30} have also been registered on the Cochrane Library at the time of writing in late 2004. These are related to the combined use of LABA and ICS in asthma, the potential superiority of the combination against ICS alone, and the potential superiority of the combination, if used together, in a single inhaler rather than in separate inhalers.

Inhaled long-acting β_2 -agonists for stable chronic asthma

This Cochrane systematic review²⁵ involved 85 studies and over 15,000 patients. Most studies were parallel-group design, and mainly involved adults with asthma of mild-to-moderate severity who were treated for between 6 weeks and 1 year (Table 2).

Table 2 Description of studies included in Cochrane reviews of long-acting β -agonist treatment.

	LABA compared with placebo	LABA compared with regular SABA	LABA compared with theophyllines
Total number of studies included	85	31	12
Total number of participants	15,245	32,967	1329
<i>Allocation concealment</i>			
Adequate	15	5	1
Unclear	70	26	10
<i>Study design</i>			
Parallel group	56	24	7
Crossover	29	7	5
<i>Participants</i>			
Adults/adolescents	7	28	12
Children less than 12 years	14	3	
<i>Period of treatment</i>			
Less than 6 weeks	32	11	7
6–24 weeks	45	19	4
25–52 weeks	8	1	1
<i>Classification of asthma</i>			
Mild	12	3	
Mild-to-moderate	51	23	1
Severe	11	3	
Unknown	11		11

LABA, long-acting β_2 -agonists; SABA, short-acting β_2 -agonists.

If the included studies are separated according to baseline treatment of asthma, then the following picture emerges: in 33 studies, participants were taking a variety of regular medications, including ICS, cromones, oral theophylline or oral corticosteroid. The total number of participants was 7927. The mean number of participants per study was 240 (range 7–614 participants). In these studies, the use of ICS ranged from 20% – 95%, with 24 studies having more than 50% of participants on ICS.

In 34 studies, all participants used ICS only as regular treatment. The number of participants was 5443. The mean number of participants per study was 143 (range 9–698 participants).

In 21 studies, participants were not allowed to take ICS. The total number included in these studies was lower at 1875. The mean number of participants per study was 89 (range 10–408 participants). The primary outcome of the review was asthma control (Table 3).

For morning peak expiratory flow (PEF), a statistically significant difference was found in favour of regular LABA over placebo, the overall weighted mean difference (WMD) being 26.8 l/min (95% CI 20.1–33.2). Sub-group analyses showed

similar positive treatment differences whether on regular ICS or not. In children, the difference was not statistically significant, but only 207 participants were included in the analysis (Fig. 1).

For evening PEF, again a statistically significant advantage was found for LABA, the WMD being 19.2 l/min (95% CI 11.6–26.7). Sub-group analyses showed similar treatment effects in people taking ICS and those on mixed co-interventions but not in people taking regular ICS or in children. Trends were in the same direction for these sub-groups, but the numbers of participants were small in the ICS-free studies ($n = 79$) and in children ($n = 207$) (Fig. 1). It is likely that the absence of statistically significant benefit in the sub-groups is due to small numbers of participants. Indeed, when assessing PEF as change from baseline, where larger numbers of participants were included in the sub-groups of children and non-ICS users, statistically significant differences were found (Fig. 2). However, for both these sub-groups, the WMD was smaller than for the overall change in either morning or evening PEF.

For FEV₁, a statistically significant benefit was found for LABA, the overall WMD being 180 ml (95% CI 130–230), with similar effects for those on mixed

Table 3 LABA in chronic stable asthma: differences in outcomes for LABA versus placebo.

Outcome	Overall			Participants not taking ICS		
	Difference	Studies	Participants	Difference	Studies	Participants
Morning PEF (l/min)*	26.78 (20.36–3.20)	19	4066	49.08 (6.22–91.95)	3	88
Evening PEF (l/min)*	19.18 (11.63–6.73)	13	3094	15.58 (–30.74–61.89)	3	79
Change in morning PEF (l/min)*	25.83 (20.48–31.17)	20	5308	19.66 (10.60–28.72)	5	1046
Change in evening PEF (l/min)*	18.14 (13.23–23.06)	17	5048	10.38 (5.82–14.95)	4	1002
FEV ₁ (l)*	0.18 (0.13–0.23)	17	3465	0.12 (–0.25–0.49)	2	70
Change in FEV ₁ (l)*	0.19 (0.16–0.23)	15	3423	0.18 (0.10–0.25)	5	1406
Day-time symptom score [†]	–0.32 (–0.40 to –0.25)	15	3084	–0.4 (–0.9–0.1)	3	79
Night-time symptom score [†]	–0.41 (–0.49 to –0.32)	10	2396	–0.4 (–0.9–0.1)	2	66
% Days without asthma symptoms*	17.06 (13.93–20.19)	14	3700	12.7 (8.6–16.8)	4	789
% Nights without asthma awakenings*	9.65 (5.67–13.64)	14	3140	8.1 (4.9–11.3)	4	789
Day-time relief SABA used (puffs)*	–0.80 (–1.14 to –0.46)	9	2474	–0.6 (–1.7–0.5)	1	23
Night-time relief SABA used (puffs)*	–0.41 (–0.60 to –0.23)	9	2478	0.1 (–1.3–1.6)	1	23
Any drug-related adverse event [‡]	1.35 (1.03–1.77)	9	1444	Not estimable	0	0
Headache [‡]	1.35 (1.01–1.81)	14	3982	1.80 (0.76–4.29)	2	452
Tremor [‡]	1.69 (0.68–4.22)	6	1695	Not estimable	0	0
Risk of more than one major exacerbation [‡]	0.78 (0.69–0.88)	27	7438	0.72 (0.52–1.00)	4	1020
Change in BHR (doubling doses)*	0.48 (0.25–0.95)	9	1181	0.62 (0.30–0.95)	4	705

BHR, bronchial hyper-reactivity; ICS, inhaled corticosteroids; PEF, peak expiratory flow; SABA, short-acting β_2 -agonists.

*WMD and 95% confidence interval (CI). Mean differences from individual trials are weighted and the inverse-variance method of meta-analysis used to obtain an overall mean difference and CI.

[†]SMD with 95% CI. The overall difference in means from studies in which the outcome is measured in different units, divided by the pooled standard deviation of participants' outcomes across the whole trial, is known as the standardized mean difference.

[‡]OR and 95% CI using the Mantel–Haenszel method, which assumes a fixed-effect model of meta-analysis.

Review: Inhaled long acting beta agonists for stable chronic asthma
 Comparison: 01 Studies with parallel group design
 Outcome: 01 Peak expiratory flow: morning l/min

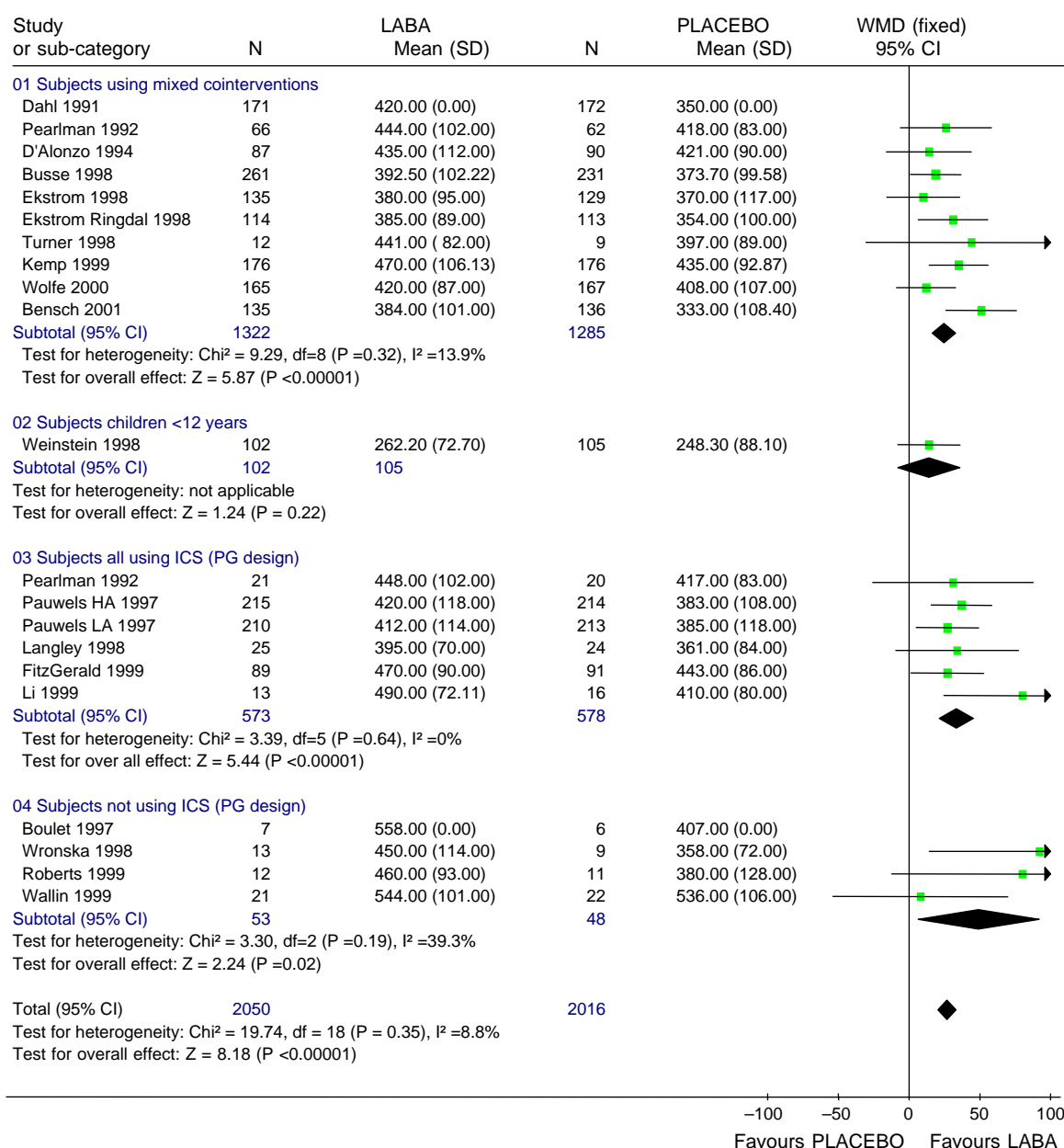


Figure 1 Effect size and pooled results for morning PEF in studies comparing LABAs with placebo.

co-treatments, those taking ICS and also for children. There was no statistically significant effect on FEV_1 for those not taking ICS, although numbers were very small ($n = 70$). A similar difference was seen for the change in FEV_1 during treatment and, for this outcome, all sub-groups, including those not taking ICS, were statistically significant, probably as a result of larger numbers of participants in the sub-groups (not on ICS: $n = 1046$).

For the outcome measures related to symptomatic control and need for relief medication, the positive outcomes for LABA were essentially similar irrespective of sub-group. The scales used to measure symptom scores ranged from 4 – 10 units and, allowing for this, the overall standardized mean difference (SMD) for day-time scores was -0.32 (95% CI -0.40 to -0.25) and night-time scores was -0.41 (95% CI -0.49 to -0.32). This equates to a difference of about 0.12 and 0.25 for

Review: Inhaled long acting beta agonists for stable chronic asthma
 Comparison: 01 Studies with parallel group design
 Outcome: 05 Change in PEF morning (l/min)

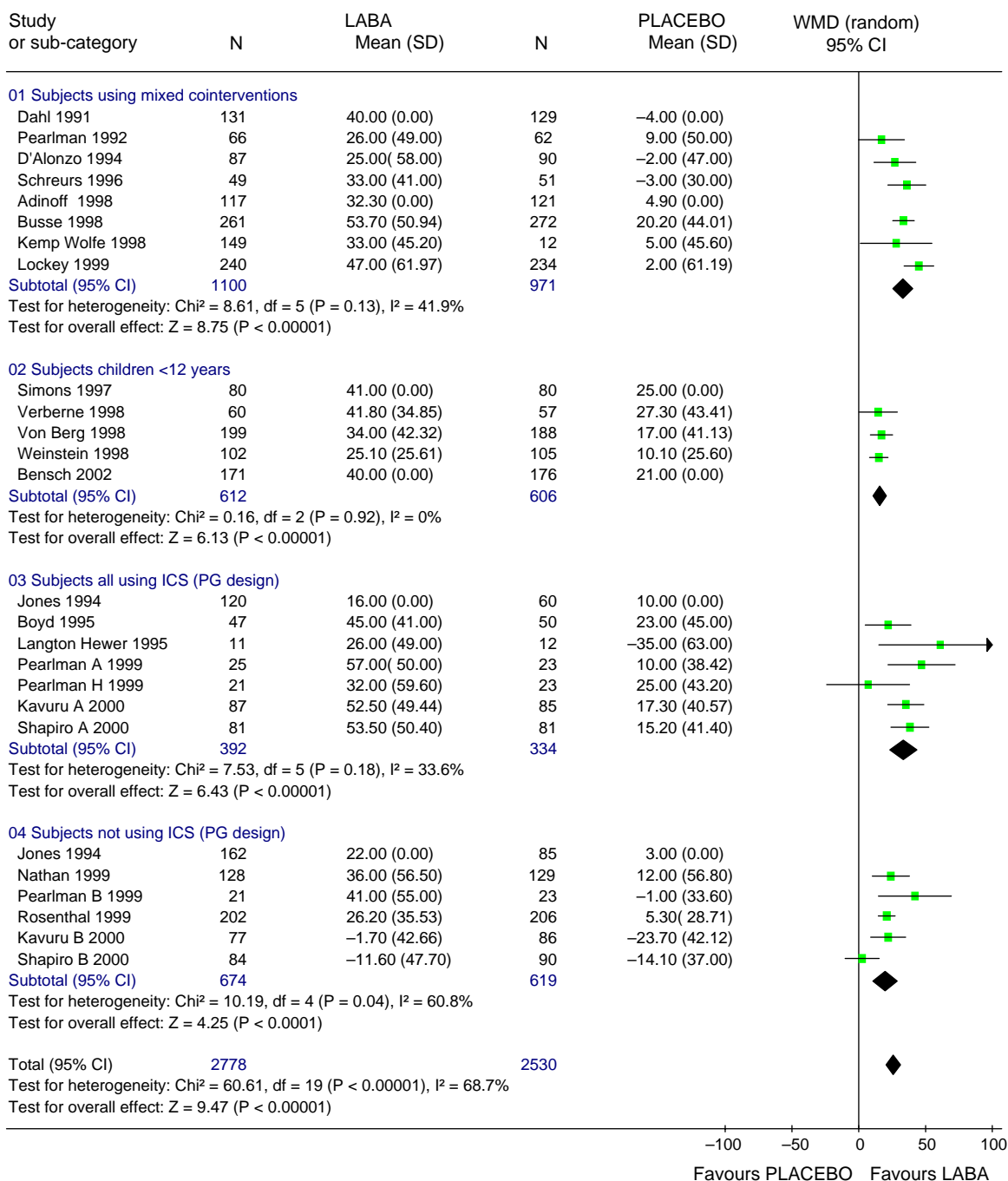


Figure 2 Effect size and pooled results for change in morning PEF in studies comparing LABAs with placebo.

day-time and night-time, respectively, on a six-point scale, favouring LABA treatment.

When people taking ICS regularly are compared with people who are not, the results show little difference, with all results in favour of LABA. This is especially so where the number of participants was reasonably robust (i.e. day- and night-time symp-

tom scores and the percentage increase in days and nights without asthma symptoms).

In addition to the expected drug-related adverse events due to known pharmacological effects of LABA (i.e. headache, tremor muscle, cramps and palpitations), the review analysed data on asthma "exacerbations"; however, they were defined in

the individual studies. When all studies with data were analysed together for any drug-related adverse effect, the odds ratio (OR) was elevated at 1.35 (95% CI 1.03–1.77) in nine studies with 2823 participants. The only individual adverse effect for which there was a significantly increased risk was headache, OR 1.35 (95% CI 1.01–1.81).

Twenty-seven parallel-group studies, with 7438 individual participants, reported data on exacerbations. In 15 studies with adult participants, a “major” exacerbation of asthma was defined as worsening of asthma symptoms requiring treatment in addition to the study drug and usual rescue inhaled SABA agent. In seven studies, the definition was not given or was less precise. Overall, there was a significant reduction in the risk of experiencing at least one major exacerbation during the study period in the LABA group compared with placebo, OR 0.78 (95% CI 0.69–0.88), with no significant heterogeneity (I^2 29.4%) (i.e. the chance of an exacerbation of asthma was decreased by about 25% overall). When the analysis was confined to 15 studies (n = 3934), with a uniform definition of a major exacerbation, the effect was even larger, OR 0.66 (95% CI 0.56–0.78), and the risk difference (RD) -0.04 (95% CI -0.05 to -0.02).

Interestingly, in four studies with a total of 1020 participants not using ICS, there was a very similar reduction in risk of a major exacerbation, OR 0.72 (95% CI 0.52–1.0), but the difference was not statistically significant. In two studies of 6 months’ duration^{31,32} using participants who had not been taking ICS during the previous 6 months, the difference in exacerbation risk between groups for steroid-naïve participants was not significant, OR 0.83 (95% CI 0.53–1.29). In both studies, around 13% of participants treated with LABA experienced at least one major exacerbation. In two studies of 3 months’ duration,^{33,34} using participants who had been taking ICS for at least 3 months but then stopped at randomization, there was a reduction in exacerbations, OR 0.58 (95% CI 0.36–0.98), RD -0.09 (95% CI -0.18 to -0.01). However, in these two studies of previous ICS users, 38% and 44%, respectively, of LABA-treated participants were withdrawn during the 3 months because of worsening asthma. In addition, the difference between the three regular background treatment sub-groups (ICS use, no ICS use and mixed co-interventions) for the outcome “risk of an exacerbation” using the Peto OR is significant (χ^2 14.3, df 2), suggesting that the result of meta-analysis needs to be interpreted with some caution.

The sub-group result in children under 12 years of age (from five studies that reported on exacerba-

tions) showed a small and non-significant increase in risk, OR 1.2 (CI 0.92–1.55) with LABA treatment.

Despite previous concerns, in an analysis of eight studies lasting at least 6 weeks in which change in bronchial hyper-reactivity (BHR) was measured as an outcome, there was a small but significant lessening of BHR in favour of LABA use. Interestingly, in the sub-group analysis, the positive effect on BHR was clearest for those taking ICS, although this may reflect increased power, because of the greater numbers in this sub-group analysis (350 of the total 600).

The following conclusions were drawn from this large review based on a broad range of studies across the asthma spectrum: (1) overall, the data gave reassuring evidence for the effectiveness and safety of LABA used regularly in chronic asthma, compared with placebo in randomized-control trials; (2) there was no evidence that underlying control of asthma deteriorated with regular use of LABA and, indeed, overall there was a decrease in exacerbation rates; (3) the evidence supports the use of LABA in addition to ICS as emphasized in current guidelines; (4) the data from the patients included in these studies also suggest that regular LABAs have some positive effects in patients not using regular ICS but without increasing the risk of exacerbations or BHR.

Regular treatment with long-acting β -agonists versus daily regular treatment with short-acting β -agonists in adults and children with stable asthma

In this Cochrane review,²⁶ most of the 31 included studies were in mild-to-moderate asthma, with participants in all but one study taking other regular co-interventions. In 24 of these 30 studies, at least 50% of participants were using regular ICS (Table 2). Again, the primary outcome was asthma control (Table 4). LABAs were significantly better than SABA for a variety of lung function measurements, including morning and evening PEF, and had significantly lower scores for day and night-time asthma symptoms and percentage of days and nights without symptoms. LABAs were also associated with a significantly lower use of rescue medication during the day and night.

The risk of exacerbations was not different between the two types of agent, but most studies were of short duration, which limited the power to test for, and assess the relevance of, such differences.

Table 4 Effects of LABA versus SABA treatment in adults and children.

Outcome	Difference	Studies	Participants
Morning PEF (l/min)*	32.93 (24.8–41.4)	8	1881
Evening PEF (l/min)*	25.62 (17.98–32.27)	8	1878
Change in morning PEF (l/min)*	27.38 (22.98–31.77)	6	2117
Change in evening PEF (l/min)*	11.94 (7.99–15.90)	6	1991
FEV ₁ (l)*	0.22 (0.14–0.31)	8	1397
Day-time symptom score*	–0.15 (–0.23 to –0.06)	3	678
Night-time symptom score*	–0.21 (–0.31 to –0.10)	3	701
% Days without asthma symptoms*	10.34 (1.80–18.88)	2	307
% Nights without asthma awakenings*	12.12 (7.80–16.43)	3	606
Day-time relief SABA used (puffs)*	–0.33 (–0.16 to –0.5)	4	1002
Night-time relief SABA used (puffs)*	–0.31 (–0.19 to –0.43)	4	1002
Overall quality of life†	0.54 (0.39–0.69)	2	727
Any drug-related adverse event‡	1.13 (0.80–1.59)	5	953
Headache‡	1.28 (1.02–1.61)	13	3737
Tremor‡	0.68 (0.43–1.07)	11	3780
Risk of more than one major exacerbation‡	0.90 (0.78–1.03)	14	28,814
Deaths‡	3.00 (0.67–13.41)	1	25,180

LABA, long-acting β_2 -agonists; SABA, short-acting β_2 -agonists; PEF, peak expiratory flow.

*WMD and 95% CI. Mean differences from individual trials are weighted and the inverse-variance method of meta-analysis used to obtain an overall mean difference and CI.

†SMD with 95% CI. The overall difference in means from studies in which the outcome is measured in different units, divided by the pooled standard deviation of participants' outcomes across the whole trial, is known as the standardized mean difference.

‡OR and 95% CI using the Mantel–Haenszel method, which assumes a fixed-effect model of meta-analysis.

Table 5 Effect of LABA versus theophyllines for maintenance treatment of asthma.

Outcome	Overall difference	Studies	Participants
Morning PEF (l/min)*	37.20 (–7.65–82.05)	1	112
Evening PEF (l/min)*	39.70 (–5.00–84.40)	1	112
FEV ₁ (% predicted)*	9.00 (7.80–10.20)	1	96
Day-time symptom score*	–0.20 (–0.49–0.09)	1	40
Night-time symptom score*	–0.10 (–0.37–0.17)	1	45
Any drug-related adverse event†	0.44 (0.30–0.63)	5	807
Central nervous system adverse event†	0.50 (0.29–0.86)	4	527
Gastrointestinal adverse event†	0.30 (0.17–0.55)	4	527

*WMD and 95% CI. Mean differences from individual trials are weighted and the inverse-variance method of meta-analysis used to obtain an overall mean difference and CI.

†RR and 95% CI using the Mantel–Haenszel method, which assumes a fixed-effect model of meta-analysis.

The following conclusions were drawn from this relatively large review: (1) LABAs have advantages in clinical outcomes when used regularly over the effects of regular inhaled SABA; (2) the increased cost of treatment, if more LABAs are prescribed, has implications for medical costs, which will only be partially offset by reduced symptom-directed use of SABA.

Long-acting β -agonists versus theophylline for maintenance treatment of asthma

In this Cochrane review,²⁷ 12 studies were included, involving 1329 participants. Nine studies used salmeterol, two used eformoterol and one used

bitolterol. In nine studies, participants were included using ICS, with an average of 60% of participants in these studies using regular ICS, whereas in three studies they were not permitted.

Unfortunately, because of lack of appropriate data, only limited meta-analyses were possible, but a number of findings were drawn from the review (Table 5): (1) LABA and theophylline are both effective in increasing lung function in asthma but, in five individual studies, LABA increased PEF significantly more than theophylline; (2) in six studies, no significant difference was found between LABA and theophylline on the increase from baseline in FEV₁ and, in two studies, salmeterol was significantly more effective; (3) LABA gave more symptom-free nights than theophylline and less need for rescue SABA medication, but these data come from individual studies as pooling was not possible because of reporting differences; (4) LABA use significantly reduced the risk of adverse events associated with theophylline use, with an overall relative risk (RR) of 0.44 (95% CI 0.30–0.63). The reduction in risk was significant for central nervous system side-effects such as headache, RR 0.50 (95% CI 0.29–0.86) and gastrointestinal side-effects, RR 0.30 (95% CI 0.17–0.55). Despite this, there was a non-significant difference between treatments for withdrawals.

The authors concluded that LABAs are as effective as theophyllines in reducing asthma symptoms and have fewer adverse effects.

These reviews confirm the effectiveness of LABA in the management of chronic asthma.

Discussion

In general, the reviews support international management guidelines in their current placement of LABA (i.e. as additional therapy when asthma is inadequately controlled by ICS at moderate dose). However, several individual studies, across a wide range of starting ICS doses, have shown that LABAs are able to keep the dose of ICS needed to control asthma below the threshold for systemic absorption, thus decreasing the potential for long-term systemic adverse effects.^{35,36} These data have yet to be combined in a systematic review or included in management guidelines.

In addition to supporting established asthma management guidelines, we are interested in how these reviews help clinicians and patients in the "real" world, with its constraints and compromises. We know from extensive analysis of therapeutic practice in the community⁵ that most

asthma is mild and uncomplicated by major exacerbations; patients may still continue to have frequent symptoms; and, in spite of their symptoms, most patients do not use ICS as prescribed.

Data in Australia suggest that about a third of patients with asthma are prescribed ICS, but only a third of them actually use them regularly—many on the basis of negative attitudes towards their medication.⁵ These considerations raise the question of whether, given their symptom levels and lack of use of ICS, such patients might be better off using regular LABA than frequent SABA.

A published systemic review³⁷ has shown that the regular use of inhaled SABA is not associated with a clinically meaningful deleterious effect on the main indicators of asthma control. Neither is there any major beneficial effect, beyond that achieved by their "as needed" use. The current reviews would indicate that if frequent airway β -receptor stimulation is required, then a long-acting agent (LABA) has distinct advantages over short-acting agents.

What then of the residual worries inherent in "the continuing β -agonist debate"? Two large post-marketing phase IV studies with salmeterol have been conducted, and need to be mentioned before finally trying to answer that question: the Serevent Nationwide Surveillance Study (SNSS)³⁸ in a general-practice setting in the UK in the early 1990s and the Salmeterol Multi-centre Asthma Research Trial (SMART) initiated in the USA by GSK in 1996.³⁹

The important points to emerge were as follows: (1) asthma mortality is related to severity of disease and reflected in high levels of use of relief bronchodilator medication; (2) underuse of ICSs in severe asthmatics is dangerous; (3) many patients classified as "mild" are still using substantial amounts of relief medication [1.2 canisters/month (i.e. 6–8 puffs/24 h in SNSS)]; and (4) LABAs are not a substitute for ICSs and should not be initiated in patients with significantly worsening or acutely deteriorating asthma.

Worries have reasonably been expressed about mortality rates in these studies. The SNSS had a three-fold increase in deaths in the salmeterol group compared with the placebo group, but the difference was not significant as the rate of "events" was low and not different from what was expected. There was no pattern of severe asthma events occurring in the salmeterol group to suggest some systematic danger signal. Indeed, there were significantly fewer dropouts due to asthma worsenings in the salmeterol group. The SMART study was stopped prematurely, but has not been published. Again, there was concern about excess mortality in the LABA limb. This seems to

have been predominantly in Afro-American participants who had more severe asthma at entry and were likely to have been undertreated with ICS.

What is uncertain from these studies is the level of asthma severity or use of SABA relief medication that should mandate the use of ICS. Current asthma management guidelines are imprecise. GINA guidelines state that "inhaled glucocorticosteroids are the most effective controller therapy, and are therefore recommended treatment for persistent asthma at any step of severity".¹ The Australian NAC guidelines² state that "symptoms should be relieved with intensive initial therapy (with ICS) and then minimum maintenance doses (of ICS) used to maintain good symptom control, minimize side-effects and maximize adherence", without specifying at what level of symptoms ICS should be introduced. UK guidelines state that "though the threshold has not been firmly established, there is evidence for their (ICS) introduction if SABA are used more than two or three times a day".³

The dilemma is exacerbated because guidelines are not well implemented in practice. To what extent should energy be directed solely at better implementation, with increased prescribing of ICS, or should we expend efforts on better recognition of patients with minimal risk of life-threatening events who could be given LABA safely in the absence of ICS? Further research on this is needed; until then, it is sensible that our focus is on better and more generalized implementation of current guidelines.

The enduring worry is that such an alternative approach could delay the use of ICS in patients who need them and, by so doing, put such patients at risk. We would certainly not want to encourage inadequate assessment and management of asthma, nor discourage use of ICS where this is appropriate. It is possible, however, that there is a group of mild relatively stable patients, not using ICS, who may be better off using LABA than repeat dosing with SABA.

Practice points

- LABAs are better than placebo in improving lung function, symptom scores and use of relief medication.
- LABAs are better than regular SABA.
- LABA do not worsen BHR.
- LABAs reduce exacerbation rates in adults.
- LABAs are better than theophyllines and have fewer side-effects.

Research directions

- Can we define a group of patients who are using SABA frequently in whom it would be safe to use LABA without ICS?
- What are the preferences of patients in this group?
- What are the safety and efficacy of LABA versus low-dose ICS in mild asthma?
- When should ICS definitely be introduced?
- What are the optimum combinations of LABA and ICS to maximize asthma control and minimize adverse effects?

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